REMARKS

Claims 1, 4-9, 52-55, 57, and 59-86 will be pending and under consideration upon entry of the above-made amendments. Claims 1, 53, 57 and 59-66 have been amended to clarify that which Applicants regard as the invention. New claims 85 and 86 have been added. The amended and new claims are fully supported by the specification as indicated below. No new matter has been added.

As a preliminary matter, Applicants note that claims 3 and 58 were cancelled in the Amendment filed August 8, 2003, but the Office Action Summary mailed October 22, 2003 identifies claims 3 and 58 as pending. Applicants respectfully request that the cancellation of claims 3 and 58 be reflected in future Office Actions.

Also, Applicants note with appreciation that the Office Action Summary mailed October 22, 2003 indicates that claims 57-65, which had been withdrawn from consideration, have been rejoined in the instant application pursuant to Applicants' request.

Claims 1, 53 and 66 are amended to recite that the lipid is an amphipathic lipid and that the preliposome-lyophilate is prepared by a method comprising lyophilizing a composition comprising an amphipathic lipid, t-butanol, water, and non-lipid surfactant.

Claim 1 is also amended to replace the recitation that the preliposome-lyophilate "has the ability to form liposomes having a median diameter of less than 1 μm," with the recitation that the preliposome-lyophilate "upon reconstitution with aqueous solution results in a distribution of liposomes having a median diameter of less than 1 μM," to clarify that the reconstitution itself results in such a distribution, without the need for any physical sizing methods.

Claim 57 is amended to specify that the lipid is an "amphipathic lipid". Claim 57 is also amended to replace the recitation of the lyophilate "having the ability to form liposomes having a median diameter of less than 400 nm upon reconstitution with aqueous solution," with the recitation that the preliposome-lyophilate "upon reconstitution with aqueous solution, results in a distribution of liposomes having a median diameter of less than 400 nm," to clarify that the reconstitution itself results in such a distribution, without the need for any physical sizing methods.

Claims 59-65 have been amended to specify that the lyopohilate is a "preliposome-lyophilate" as recited in base claim 57.

Claim 66 is further amended to include the phrase "distribution of" before the

term "liposomes."

Support for the amended claim recitations and for the new claims is found in the specification, for example, as set forth in the table below (citations being to the page and line numbers of the instant application).

Claim No.	Support
1	Page 4, lines 23-25; page 8, lines 24-25; and page 32, lines 21-22.
53	Page 4, lines 23-25; and page 32, lines 21-22.
57	Page 5, lines 10-12; page 10, lines 20-21; page 11, lines 3 and 14-17; and page 32, lines 21-22.
66	Page 4, lines 23-25; page 10, line 27; and page 32, lines 21-22.
85	Page 32, lines 21-23.
86	Page 32, lines 21-23.

Rejections Under 35 U.S.C. § 112

Claims 1, 4-9, 52-55 and 66-84 have been rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Specifically, the Examiner states that "[l]yophilization is a specific process which removes only water and volatile organic solvents. The independent claims 1 and 66 recite no water at all." The Examiner contends that "[a] review of the specification indicates that the use of a phospholipid and a surfactant dissolved in t-butanol and water and the [sic] this product is then lyophilized," and suggests "reciting the process steps including t-butanol and water, a phospholipid and the surfactant."

Applicants have amended independent claims 1, 53 and 66 to recite that the lyophilate was made by a method comprising lyophilizing a composition comprising at least one amphipathic lipid, t-butanol, water, and non-lipid surfactant. Applicants have also amended claims 1, 53 and 66 to recite that the lipid is an amphipathic lipid. Applicants note that the use of "amphipathic" lipids to make liposomes is well-known in the art, and therefore, the claims need not be limited to phospholipids as suggested by the Examiner.

Accordingly, the rejection of claims 1, 4-9, 52-55 and 66-84 under 35 U.S.C. § 112, second paragraph, has been overcome in view of the amendments to claims 1, 53 and 66, and the rejection should be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1, 4-9, 52-55, 57 and 59-84 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 4.950,432 to Metha et al. ("Mehta I") or U.S. Patent No. 5,811,119 to Mehta et al. ("Mehta II"), further in view of U.S. Patent No. 5,585,112 to Unger ("Unger"), U.S. Patent No. 5,089,602 to Isliker ("Isliker"), or U.S. Patent No. 5,653,996 to Hsu et al ("Hsu"), individually or in combination.

Applicants respectfully disagree with the Examiner's rejection. To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). Secondly, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *M.P.E.P. 2143.* As discussed in Amendment filed August 8, 2003 and detailed below, there is no suggestion or motivation either in the references cited by the Examiner themselves or in the knowledge generally available to one of ordinary skill in the art to modify the references or to combine the teachings of the references to arrive at the presently claimed invention. In addition, none of the references cited by the Examiner, individually or in combination, teach or suggest all the claim limitations.

None of the references cited by the Examiner disclose or suggest a lyophilate with lipid and non-lipid surfactant, which lyophilate was made by lyophilizing a composition that did not contain any liposomes at the time of lyophilization, but which produces a submicron distribution of liposomes as a result of reconstitution. Applicants note that the claims have been amended to clarify that the submicron distribution is a result of reconstitution (i.e., not of physical sizing methods). In contrast, the prior art references teach that to achieve a lyophilate that produces a submicron distribution of liposomes upon reconstitution, one first had to make liposomes, then use physical sizing methods (e.g., filter extrusion under pressure) to achieve a submicron size distribution of the liposomes, and then lyophilize. The claimed lyophilate differs in composition from these prior art lyophilates

because no liposomes were present at the time of lyophilization, and was achieved based upon the inventors' discovery that the use of surfactant as taught in the instant specification unexpectedly allows the skilled artisan to achieve liposomes of submicron distribution without having first to make liposomes and then to size them. This is explained in more detail below with respect to the references cited by the Examiner.

Both Mehta I and Mehta II fail to teach liposomes of submicron distribution, much less a lyophilate, not made from liposomes, that provides the same. See e.g., Mehta II at col. 8, lines 19-21, which discloses a larger size distribution. Both Mehta I and Mehta II also fail to teach the use of a non-lipid surfactant in a lyophilate that lacked any liposomes at the time of lyophilization (or in any lyophilate).

Unger is concerned with gaseous precursor-filled liposomes. Unger teaches the use of physical sizing means exerted on liposome preparations to achieve submicron distributions of liposomes, and contains no hint or suggestion of a lyophilate, not made from liposomes, that provides a submicron distribution. See e.g. Examples 14 and 15 (col. 45, line 29 to col. 46, line 7) of Unger, wherein liposomal suspensions are extruded under pressure through a membrane or passed through a microfluidizer in order to generate submicron size distributions; and col. 26, lines 31-40 of Unger which describes methods of sizing including filtration, extrusion, sonication, homogenization, and introducing a laminar stream of a core of liquid into an immiscible sheath of a liquid. Unger expressly teaches that "[e]xtrusion under pressure through pores of defined size is a preferred method of adjusting the size of the liposomes" (col. 26, lines 55-57 of Unger). Although Unger discloses the use of non-ionic surfactants to increase stability of the gaseous precursor-filled liposomes (col. 25, lines 38-48), and the use of emulsifying agents (col. 23, lines 20-47), Unger does not teach that surfactants can be used to achieve a submicron distribution of liposomes in the absence of physical sizing methods conducted upon liposomes, and thus does not hint or suggest a lyophilate which provides a submicron distribution upon reconstitution but which differs in composition from the prior art lyophilates since it did not contain liposomes at the time of lyophilization.

Regarding Unger's use of the surfactant sodium lauryl sulfate ("SLS") (see Example 10 of Unger), as would be known by one skilled in the art, SLS has a high hydrophile-lipophile balance (~40), and thus the skilled artisan would not have been motivated to use SLS as a surfactant for an application whose goal is the formation of a stable

oil-in-water type emulsion of the type that would be necessary to provide small liposomes (see Amendment filed August 8, 2000).

Isliker also does not remedy the deficiencies of the above-discussed references, since Isliker also does not teach a submicron distribution of liposomes achieved without physical sizing of liposomes, and thus also does not suggest a submicron reconstitute lyophilate that did not contain liposomes at the time of lyophilization.

Isliker is directed toward a process for the isolation of apolipoproteins from blood plasma. The apolipoproteins can be put in proteoliposomes (col. 5, lines 12-16) and are used for treatment of cardiovascular disease (col. 5, lines 65-68). While Isliker discloses the use of surfactants for the deaggregation or solubilization of lipoprotein aggregates during purification (col. 3, lines 28-34; col.4, lines 58-64), Isliker neither teaches nor suggests a lyophilate which does not contain surfactant at the time of lyophilization. Moreover, Isliker teaches the removal of surfactant prior to lyophilization (see col. 4, lines 61-64 and col. 8, lines 47-51). Therefore, Isliker does not cure the deficiencies of Mehta I or Mehta II, alone or in combination with Unger, since Isliker teaches neither a lyophilate which is free of liposomes at the time of lyophilization, nor a lyophilate which even contains surfactant.

Hsu teaches methods for the preparation of liposomes utilizing the aerosolization of a solution comprising bilayer forming materials and optional additional molecules onto an aqueous surface. While Hsu discloses the use of surfactants in making liposomes, Hsu does not teach that surfactants can be used to achieve a submicron distribution of liposomes in the absence of physical sizing methods conducted upon liposomes, and thus does not hint or suggest a lyophilate which produces a submicron distribution upon reconstitution but which differs in composition from the prior art lyophilates since it did not contain liposomes at the time of lyophilization. In contrast, Hsu teaches physical sizing methods conducted upon liposomes in order to achieve submicron distribution (see col. 11, line 43 to col. 12, line 3). Thus, Applicants contend that the present invention is not obvious over Mehta I or Mehta II in light of Hsu, alone or in combination with the other cited references. Further, the Hsu reference was discussed during the interview conducted on March 23, 2004, and Examiner Kishore agreed with Applicants' interpretation of Hsu, stating that he did not feel that Hsu, alone or in combination with Mehta I or Mehta II would make the presently pending claims unallowable.

In view of the foregoing, Applicants respectfully assert that the rejection of

claims 1, 4-9, 52-55, 57 and 59-84 under 35 U.S.C. § 103(a) is in error and respectfully request that it be withdrawn.

CONCLUSION

Applicants respectfully request that the present amendment and remarks be entered and made of record in the instant application. It is submitted that all the outstanding rejections have been obviated or overcome. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Enclosures